INFECTIONS IN INTENSIVE CARE PATIENTS: USE OF NEW B-LACTAMS*

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Although many highly effective antimicrobial agents have been discovered or synthesized during the past 50 years, the fight against infection is far from over. Indeed, the new battleground has shifted to the hospital and to intensive care patients. The major improvements in sanitation and hygiene have reduced such diseases as typhoid and cholera. However, infections in intensive care patients will not decline as these other diseases have. The reason is that the present problem, nosocomial infections in critically ill patients, differs in many ways. Infections in these patients result not only from failures in infection control, but the infections result from acquisition of bacteria or fungi which, becoming endogenous, cause infection or invade the host as a result of our very care of the patient. It is important to realize that infections will not vanish with improved sanitation techniques.[1] Antibiotics will be required to treat infections.

Bacteria such as *Serratia, Pseudomonas, Acinetobacter,* and *Enterobacter* have become important in intensive care units as a result of major improvement in the care of patients with cardiac, renal, hepatic, hematologic, and traumatic diseases. Patients who two decades ago readily succumbed to infection do not die within three days of admission to the hospital. Rather they live on attached to respirators, cardiac monitors, or dialysis machines to become infected and to be the source of infection of other patients.

There has been an increased awareness during the past decade of the importance of the patient in the acquisition of infection.[2] It is apparent that

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the individual whose mucocutaneous defenses are bypassed by intravenous or urethral catheters is in a situation in which it is easier for organisms to enter the body. It is also apparent that individuals who have defects of host protection whether these be immunoglobulins, T-cells, or, most important, white cells, are much less able to cope with the problem of organisms which have colonized their body surfaces. We now know that Gram negative bacteria have surface structures which allow them to adhere to respiratory, gastrointestinal, and urogenital epithelial cells. Healthy individuals are less readily colonized by such enteric bacteria as *Escherichia coli, Klebsiella,* and *Proteus,* or by staphylococci. Colonization precedes invasion and infection. The healthy individual may have a transient bacteremia from an improperly cared for catheter, whether vascular or urologic, but he will often be rid of the organism before proper therapy is even instituted. Thus, in considering the role of new antibiotics during the 1980s, it will be necessary to consider three aspects: the bacteria, the patient and the environment.

Mechanisms of Resistance to Antimicrobial Agents

Many mechanisms have been proposed by which bacteria evade destruction by antimicrobial agents. All of these mechanisms can perhaps be incorporated into three categories: alteration in transport system or permeability, enzymatic inactivation, and alteration of a target site by synthesis of a resistant or alternate target.

The first type of mechanism involves an alteration in either the cell wall or the cell membrane so that a compound fails to reach its receptor site. This change could occur in various ways. For example, a change in the outer wall configuration could prevent the entry of highly charged molecules. In Gram negative bacteria, molecules may enter through spaces between porin proteins (proteins that line channels in cell walls) in the outer membrane.[3] Changes in the lipid content of the bacteria or in the binding together of the cell wall by the cations calcium and magnesium can affect the entry of an agent and thereby cause resistance. This phenomenon has been shown to occur in pseudomonads and *E. coli.* More common, however, is reduced uptake or increased removal of an agent. With the tetracylines in the *Enterobacteriaceae,* this is a plasmid mediated function.[4] Phosphonic acids fail to enter bacteria that have an altered glycerol phosphate transport system. Although most authors have considered the aminoglycoside modifying enzymes components of a degradataive

mechanism, it is now clear that enzymatically modified drugs do not induce a transport protein as do normal aminoglycosides, and the modfied aminoglycosides are not transported across the cytoplasmic membrane to their receptor site on the 30S ribosomes. Aminoglycosides do not inhibit anaerobic bacteria because they fail to enter those organisms that lack an energized membrane.

The second type of resistance mechanism, enzymatic inactivation of antimicrobial agents, is best exemplified by the β-lactamases. These enzymes, which can be plasmid mediated or chromosome mediated, have been found in virtually all bacteria, Gram positive and Gram negative. Chloramphenical transacetylase, which may be either constitutive or inducible, is the only degradative enzyme that exists inside the cytoplasmic membrane. The β-lactamases and aminoglycoside modifying enzymes (adenylating, phosphorylating and acetylating) exist in the periplasmic space of Gram negative bacteria.

The third category of mechanism, alteration of the antimicrobial target, can operate in either of two ways—through synthesis of resistant targets or through synthesis of a resistant metabolic pathway. Although mutation is the most frequent mechanism of change in the antimicrobial target, plasmids also can cause such a change. Resistance to erythromycin and lincomycin in staphylococci is due to the production of methylated 23S RNA. The resistance of *Bacteroides fragilis* to clindamycin has been shown to be plasmid mediated and transferable. The presence of an altered DNA gyrase in *Enterobacteriaceae* accounts for the resistance of these organisms to nalidixic acid, and altered DNA-directed RNA polymerase produces resistance to rifampin.

The most interesting instances of resistance caused by altered target sites are those stemming from the alteration of penicillin-binding proteins in *Neisseria gonorrhoeae* and *Streptococcus pneumoniae* in South Africa. Methicillin resistance in *Staphylococcus aureus* probably is also due to altered penicillin-binding proteins.

Enterobacteriaceae resistant to trimethoprim have an altered dihydrofolate reductase, and resistance to sulfonamides is due to an altered dihydropteroate synthatase that allows the organisms to bypass the competitive inhibition of these drugs.

Genetic basis of resistance. Although mutation can cause resistance, it is in general ineffective, both because only a single trait is involved and because alteration of a metabolic pathway may increase division time or

alter other properties of a microorganism. In contrast, the introduction of extrachromosomal DNA in the form of a plasmid can make a microorganism resistant to multiple agents simultaneously, even if those agents belong to disparate classes, so that resistance involves different mechanisms.[5]

Basically, plasmids are self-replicating particles of DNA, only 2% as large as the chromosome. A particular organism can have anywhere from one to 100 plasmids. Plasmids are important mediators of antibiotic resistance because they can transport genes for resistance from one organism to another, irrespective of the species. They do not require recombination with a replicon once they have entered a bacterial organism. Further, many plasmids can enter bacterial viruses and be transmitted to other bacterial species by this vector. Plasmids carry in their DNA the ability to be infectious. In the bacteria they infect, they mediate production of the ability to mate (conjugate) with other bacteria. The fact that plasmids can conjugate allows spread of resistance through susceptible organisms. Antibiotics exert a selective pressure toward maintenance of these organisms which otherwise would tend to die off. It is fascinating that plasmid mediated bacterial resistance to heavy metals such as mercury, cadmium, and silver also has been detected. This is important because such agents would no longer be adequate as disinfectants and because extensive use of such agents as silver and iodine in hospitals might encourage the development of plasmids mediating resistance.

Mechanism of β-lactam action. The classic concept of the action of a β-lactam antibiotic upon bacteria has been that the molecule causes lysis by disrupting the cell wall architecture, which maintains the higher osmotic environment of the organisms. Such a concept was adequate for *S. aureus*, but the effects of β-lactam compounds in fact range from inhibition of cell growth (including the production of round forms or filaments) to cell death and lysis. Factors that determine the susceptibility of bacteria to β-lactam drugs are: the rate at which the specific β-lactam compound penetrates the outer wall to reach a target, the presence, type, and specific activity of β-lactamase in the microorganism, and the effectiveness of the β-lactam antibiotic in inhibiting a target site in peptidoglycan synthesis (binding to a penicillin binding protein).

Most "third-generation" cephalosporins do not owe their great activity to the ease with which they enter Gram negative bacteria. Ability of an agent to enter bacteria must be related to β-lactamase activity because

TABLE I. BACTERIAL SPECIES IN WHICH THE TEM-1 (RICHMOND-SYKES IIIA) β-LACTAMASE IS FOUND

Acinetobacter calcoaceticus	*Providencia rettgeri*
Aeromonas	*Providencia stuartii*
Alcaligenes	*Pseudomonas aeruginosa*
Citrobacter freundii	*Pseudomonas putida*
Enterobacter aerogenes	*Salmonella typhi*
Enterobacter cloacae	*Salmonella* sp.
Escherichia coli	*Serratia marcescens*
Haemophilus influenzae	*Shigella flexneri*
Neisseria gonorrhoeae	*Shigella sonnei*
Morganella morganii	*Vibrio cholerae*
Proteus mirabilis	*Yersinia enterocolitica*
Proteus vulgaris	

slow entry of an agent can lengthen its exposure to a β-lactamase and thus result in its destruction.

β-lactamases. β-lactamases of Gram positive bacterial species are primarily extracellular, inducible enzymes. In *S. aureus* they are plasmid-mediated. In Gram negative bacteria, β-lactamases are produced constitutively in the periplasmic space (when plasmid mediated) or are induced (when chromosome mediated) but still detectable in the periplasm of the cell. β-lactamase genes may be located in the plasmid or in the chromosome in different organisms of the same species.[6] Some bacteria can carry two β-lactamase genes—one chromosomal, the other plasmid.

Studies have shown that of the plasmid β-lactamases the TEM-1 enzyme is the most frequently encountered, occurring in many species of bacteria (Table I). β-lactamases are characterized on the basis of differences in activity against various β-lactam compounds and by their isoelectric points.

For practical purposes, all Gram negative bacteria have β-lactamases. The slowly entering β-lactam agent will survive only if it is highly stable, otherwise all of the agent will be destroyed by β-lactamase strategically placed in the periplasmic space. Even a β-lactam compound that readily enters the organism can be ineffective if it is easily destroyed by β-lactamases, that is, if the enzyme has a particularly high affinity for the compound. Further, some β-lactam agents induce the production of more β-lactamase. The enzyme, released into the milieu as the antibiotic kills some bacterial cells, destroys the rest of the drug and allows growth to resume.

Among the new cephalosporins, cefotaxime is stable to the plasmid β-

lactamases that hydrolyze ampicillin, the isoxazolyl penicillins, and/or cephalothin (Table II).[7] It is also stable to hydrolysis by the common and important β-lactamases encountered in *E. coli, Enterobacter, Klebsiella,* and indole-positive *Proteus*. The *in vitro* activity of cefotaxime correlates with its β-lactamase stability. Cefotaxime inhibits bacteria resistant to ampicillin, cefazolin, and carbenicillin and, most important, inhibits a number of organisms resistant to the "second generation" cephalosporins: cefamandole, cefuroxime, and cefoxitin. Cefotaxime is more stable to the β-lactamases of *Bacteroides fragilis* than are agents such as cephalothin or cefamandole, but it is less stable than such compounds as cefoxitin or moxalactam, in which the methoxy group is actually attached to the β-lactam ring.

Penicillin-binding proteins. Identification of killing targets for β-lactam antibiotics resulted from development of convenient methods to detect and study the proteins to which the β-lactam agents bind.[8] Proteins to which β-lactam drugs other than pencillin G bind can be determined by studies of the inhibition of binding of radioactive penicillin G in the presence of other agents. At the highest concentration, most β-lactam compounds lyse Gram negative bacteria such as *E. coli;* at low concentrations cell division may be maintained but results in the production of filaments. There appear to be three essential penicillin binding proteins. PBP 1_a and PBP 1_b can substitute for each other. These proteins are involved in cell elongation, and their inhibition results in structures that subsequently lyse. PBP 2 is involved in the rod morphology of *Enterobacteriaceae*. PBP 3 is necessary for cell division and, as has been noted, binding of a β-lactam drug to this protein produces long filaments.

New agents such as cefotaxime have a particularly high affinity for the penicillins binding protein of *E. coli* and other bacteria. The high binding affinity of cefotaxime for PBP 1a, 1b, and 3 undoubtedly contributes to the drug's high levels of antimicrobial activity and explains in part its activity against bacteria that it penetrates or that possess β-lactamases that partially hydrolyze cefotaxime. The higher concentrations of cefotaxime required to inhibit *S. aureus* and *S. epidermidis* are the result of a lower level of binding to the penicillin binding proteins of these species.

Nosocomial Infections

Nosocomial infections can be conveniently divided into those that are epidemic and those that are endemic. Organisms may be the same in both

TABLE II. STABILITY OF NEW CEPHALOSPORINS TO β-LACTAMASES
RELATIVE HYDROLYSIS*

β-lactamase	Cefamandole	Cefuroxime	Cefoxitin	Cefotaxime Cefizoxime Cefmenoxime† Ceftriaxone	Ceftazidime	Moxalactam	Cefoperazone
TEM-1†	36	<1	<1	<1	<1	<1	50
TEM-2†	37	<1	<1	<1	<1	<1	60
OXA-1†	—	10	<1	10	5	<1	20
OXA-2†	29	—	<1	<1	5	<1	80
OXA-3†	—	—	<1	<1	5	<1	50
P99 *Enterobacter*	13	15	<1	15	5	<1	1
Klebsiella, K1	48	<1	<1	10	5	<1	5
SHV-1†	8	<1	<1	0	<1	<1	70
Pseudomoras SA	4	<1	<1	1	<1	<1	3
Staphylococcus aureus†	5	<1	<1	0	<1	1	30
PSE-1†	43	50	25	0	0	0	15
PSE-2†	—	50	30	20	30	10	160
PSE-3†	—	—	<1	15	10	10	230
Bacteroides fragilis	160	100	<1	2	1	<1	75

*Based on rate of 100% for cephaloridine. Comparisons can only be made across the table.
†Plasmid-mediated.
††Minor differences are seen for these agents.

TABLE III. CAUSES OF EPIDEMIC AND ENDEMIC NOSOCOMIAL INFECTIONS*

	Epidemic	*Endemic*
	%	
Staphylococcus aureus	12	10
Enterococci	<1	10
Escherichia coli	3	19
Pseudomonas	4	9
Proteus	<1	8
Klebsiella	3	8
Enterobacter	7	4
Serratia	8	2
Salmonella	11	0
Streptococcus pyogenes	3	2

*Modified from Stamm et al.[9]

TABLE IV. BODY AREAS IN WHICH NOSOCOMIAL INFECTIONS DEVELOP*

Site	*Epidemic*	*Endemic*
	%	
Urinary tract	10	38
Surgical wounds	9	27
Pneumonia	12	16
Skin infections	11	6
Bacteremia	16	4
Meningitis	6	—

*Modified from Stamm et al.[9]

situations but there are important differences. *S. aureus* has been by far the most common organism seen in epidemic infections.[9] *Enterobacter* and *Serratia* have been the source of hospital outbreaks, and it is probable that *Klebsiella* was more frequent in the early 1970s, whereas recently *Serratia* has become much more important. Within the last few years, epidemics of *Corynebacterium* JK and of methicillin-resistant *S. epidermidis* have occurred. *Pseudomonas* as a cause of epidemics has accounted for about 4% of all outbreaks, but as an endemic organism it has accounted for 10% of hospital associated infections (Table III). We rarely see *S. faecalis* as a cause of an epidemic, but it is a major endemic problem on surgical services and seems to be increasing with use of some of the broad spectrum cephalosporin antibiotics such as moxalactam.

The body sites of nosocomial infections are different if the problem is one of an epidemic or rather a constant endemic problem (Table IV). Urinary tract infections are the most common endemic nosocomial prob-

TABLE V. MICROORGANISMS CAUSING NEONATAL INFECTIONS

Gram positive	*Gram negative*
Staphylococcus aureus	*Klebsiella pneumoniae*
Group B streptococci	*Klebsiella oxytoca*
Group A streptococci	*Enterobacter cloacae*
Group D streptococci	*Serratia maracescens*
	Citrobacter diversus
	Proteus mirabilis
	Pseudomonas aeruginosa
	Flavobacterium

lem; whereas bacteremia is the most common epidemic nosocomial infection. On surgical services, wounds are a major problem that can range from minor to life threatening such as necrotizing fasciitis. It is probable that nosocomial skin infections are more often an endemic problem rather than an epidemic one if one considers all of the decubitus ulcers present in any major hospital. Nosocomial meningitis is an endemic problem not unlike pneumonia[10] that develops in postoperative surgical patients.

Of particular importance has been that staphylococci during recent years have become increasingly resistant to methicillin in some parts of the world and that *Enterobacteriaceae* since the 1970s have been resistant to such agents as ampicillin, carbenicillin, and first generation cephalosporins. Analysis of data of the sites and causes of nosocomial infections has provided means to recognize outbreaks earlier and to institute therapy more rapidly, thereby reducing the size of the epidemic and reducing mortality and morbidity among those infected.

NEONATAL INFECTIONS

Although most neonates do not develop infection, the "high risk" newborn who is forced to stay for longer periods in the hospital tends to acquire Gram negative bacilli and to develop infection (Table V).[11] Neonates become colonized in the oropharynx or intestine with Gram negative bacilli the longer the infant stays in the intensive care areas. These bacilli often are multiply resistant to antibiotics as a result of heavy use of antibiotics in neonatal units. Once infants are colonized by resistant bacteria, they may shed the bacteria in their stool and transmit bacteria to the hands of workers in the units. These workers cause other babies to become colonized and some will develop infection. It is extremely difficult to break this cycle of infection-colonization-transmission because

critically ill babies in the unit always require antimicrobial therapy. Nosocomial infection due to *Klebsiella* resistant to many of the aminoglycosides have been recorded.[12]

Will the new cephalosporins play an important role in the treatment of nosocomial neonatal infections? The new agents will be important because they enter cerebrospinal fluids and nosocomial Gram negative meningitis may be treated earlier. Conversely, we may see the development of resistant *Citrobacter* species and *Enterobacter* species which are able to either destroy some of the new cephalosporins or to survive by trapping the antibiotic and in effect removing it before it reaches its target, the penicillin binding proteins. There may be a reason to prefer agents such as cefotaxime in neonates because of the problem of nosocomial group B streptococcal infections. If moxalactam were used it would be necessary to combine it with ampicillin. Use of some of the newer agents may lead to more enterococcal infections. Enterococcal osteomyelitis, meningitis, and even pneumonia have been reported among neonates. Until we have a much larger experience with use of the new cephalosporins, it will be wise to use them cautiously. It had been hoped that use of moxalactam and ampicillin would result in a better prognosis in neonatal meningitis. This has not been the case in the third neonatal meningitis cooperative study in which amikacin plus ampicillin was compared to moxalactam plus amikacin. The mortality was virtually the same (14% and 18%) and the cerebrospinal fluid was not cleared more rapidly.

Nosocomial infection in adult patients: nosocomial pneumonias. Nosocomial pneumonias are a major problem in many different patients admitted to intensive care units. Pneumonias are seen in alcoholics admitted originally with pneumococcal pneumonia, in patients with trauma and surgery, in patients with neutropenia and hematologic malignancy. Nosocomial pneumonias cause death as well as extended hospital stays.[9] Of 200 deaths at the Columbia-Presbyterian Medical Center and the Hackensack Hospital, a community hospital nearby, there were 88 nosocomial infections in 63 patients. Deaths of 52 (26%) patients were due to nosocomial infection and, of most importance, lower respiratory tract infections made up 31 or 15.5% of all deaths. If one uses such data on a national scale, at least 135,000 patients each year in the United States die of nosocomial pneumonia. Data from intensive care units have shown that 25 to 35% of patients in such units develop pneumonia after admission. Patients who develop pneumonia in an intensive care unit have

a 50% mortality rate compared to the patients who do not develop pneumonia.

Techniques to prevent colonization of the oral pharynx have not so far been successful and fully 25% of patients who become colonized by Gram negative bacteria will develop pneumonia. When pneumonia occurs in this setting, it is most often due to resistant Gram negative bacteria aspirated from the oropharynx along with the usual oral flora. Although aminoglycosides have been extensively used in nosocomial pneumonia, I have been singularly disappointed in their efficacy. Instillation of aminoglycosides into the lung may be useful in selected settings, but we have not employed this except when there is little risk of causing an outbreak of resistant bacteria. Excessive use of aminoglycosides by this essentially topical route can increase resistant bacteria in a unit.

The use of new cephalosporins or new penicillins in nosocomial pneumonias is very small. There have been cures with *Klebsiella, E. coli,* and even *Serratia.* There are encouraging results from the use of azlocillin and piperacillin, but it is too early to say with confidence that these agents will solve the *Pseudomonas* problem any more than it has been solved by ticarcillin. Whether the combination of two β-lactams such as cefotaxime and azlocillin would be preferable to the usual aminoglycoside plus antipseudomonas penicillin combination is not yet answered. I believe that considerably more work will have to be done with nosocomial pneumonia better to define subsets of patients in whom there can be the most profitable use of the new cephalosporins.

Nosocomial Urinary Tract Infections

Urinary infections still are the predominant nosocomial infection in any part of the hospital. Recent analyses of the long term effects of nosocomial urinary infection suggest a greater morbidity and mortality from nosocomial urinary infections than had been suspected. *E. coli* remains the most common organism causing urinary infections in hospitals, accounting for 50% of infections. The other organisms cannot be easily classified but *Klebsiella, Pseudomonas, Serratia,* and *Proteus* are all common. Enterococci and *Candida* must not be overlooked because they too are important organisms in intensive care units. It seems unlikely that we shall significantly reduce the incidence of urinary infections below the present figures because risk factors for the development of these infections cannot be eliminated. These factors are advanced age, debilitation, and urethral

catheterization—factors common to all patients in intensive care units. Burke and colleagues[13] have also shown that improved catheter care does not reduce infections. The one mechanism to reduce infection may be to utilize more intermittent catheterization and to avoid clusters of catheterized patients. By these two techniques we have markedly reduced nosocomial urinary infections on our neurological service. But these techniques do not work in an intensive care unit where catheterization is necessary to monitor renal viability. The new cephalosporins have a role in the therapy of nosocomial infections. These agents produce adequate urinary concentrations even when creatinine clearances falls to levels as low as 20 ml/min. This is in contrast to the aminoglycosides where we have noted that it is not possible to eradicate urinary bacteria unless urine levels are at least 30-fold greater than the minimal bactericidal concentration. Further, the very patient most prone to develop a nosocomial urinary tract infection is the one least able to withstand the possible toxicity of the aminoglycoside therapy. The marked fluid shifts and hypotensive episodes combined with the need to use loop diuretics place an intensive care unit patient at particular risk to develop nephrotoxicity. No antimicrobial agent will eliminate urinary organisms if indwelling tubes or major structural abnormalities of the urinary tract are present. I should also note that, irrespective of the agent used, the cure rates of infection in patients with *Pseudomonas* urinary tract infection rarely exceed 75%.[14] Thus, we have not completely solved the problem of nosocomial urinary infection.

There may be distinct hazards to the use of the new cephalosporins in treating urinary infection. The hazards are the development of enterococcal infections and of *Candida* superinfection or, finally, of resistant *Pseudomonas* infection.[15] These risks must be borne in mind when contemplating treatment of asymptomatic infection due to a multiply resistant organism in a patient in whom it is unlikely that the catheter will ever be removed.

Nosocomial Bacteremia

Most nosocomial bacteremias in an intensive care unit may be an endemic problem or due to contamination of some device used in the unit that produces an epidemic. The source of intensive care unit bacteremias are postoperative wounds, urinary tract, intra-abdominal infection, and pneumonias. Device-related bacteremias have been a real problem during the past decade. It is clear that the organisms which cause bacteremia can

be divided into those that occur endemically and those which for the most part are epidemic problems.[16,17] For example, *Klebsiella* causes both endemic and epidemic bacteremias. By contrast, *Enterobacter* and *Serratia* occur more as an epidemic problem, and such uncommon *Pseudomonas* species as *P. cepacia* and *P. maltophila* are nearly always epidemic problems. It would be extremely important to remember that nosocomial *S. aureus* bacteremia has not vanished during this decade and that *S. epidermidis* has become extremely important in patients with indwelling vascular catheters for chemotherapy or nutrition.

It is unlikely that endemic nosocomial bacteremias will decline during this decade. The predisposing factors of advanced age, multiple trauma, burns, underlying serious disease requiring confinement in intensive care units, and use of invasive devices will not cease.

The role of the new penicillins and cephalosporins in the treatment of bacteremia is a matter of the host involved. Agents such as cefotaxime, moxalactam, or ceftazidime would be adequate initial treatment for many bacteremias in patients who are not neutropenic. This is because the organisms most often involved, *S. aureus, E. coli, Klebsiella, Enterobacter, Serratia,* and even many *Pseudomonas* would be cleared from the bloodstream. One could not use azlocillin, mezlocillin, or piperacillin as a single agent. Knowledge of the source of the bacteremia should influence choice of antibiotic. Mortality is very low if the source of the bacteremia is the urinary tract or a vascular catheter. A markedly debilitated individual with poor white cell function who has an intra-abdominal source of bacteremia with organisms acquired in a surgical intensive care unit may well require combined therapy for the first 24 hours since there may be a polymicrobial bacteremia. If I knew that there was an infection problem with *Acinetobacter* as a cause of bacteremia in a unit, I would not use only a new cephalosporin since these agents do not inhibit *Acinetobacter.*

Nosocomial Skin Structure and Bone Infections

Too little attention has been given to the development of nosocomial skin infections in intensive care unit patients. Elderly debilitated patients often have a serious decubitus ulcer which will be the source of development of bacteremia, urinary tract infection, osteomyelitis, or even meningitis. Organisms involved frequently include *Enterobacteriaceae, Pseudomonas,* anaerobic species, and enterococci. Aminoglycosides have often proved ineffective in such infections. Unfortunately, these infections are

just the type from which resistant *Pseudomonas,* enterococci and *Candida* have been encountered.[18,19] Although there may be initial success in treating infections of the deep skin layers with the new cephalosporins, I suspect that resistant bacteria will become a problem.

The outlook for treatment of nosocomial septic arthritis and osteomyelitis is good. The new agents are not toxic as are the aminoglycosides, and the new cephalosporins permit long periods of therapy without fear of otic or nephrotoxicity. The new agents provide a means to treat resistant *Klebsiella* and *Serratia.* At the present time cefotaxime and cefoperazone probably are not adequate to treat *Pseudomonas* disease, but azlocillin, piperacillin, or ticarcillin could be used.

Nosocomial Meningitis

Klebsiella and *E. coli* are the most common causes of nosocomial meningitis.[20] Cure with chloramphenicol is extremely infrequent. Drugs such as cefotaxime and moxalactam have an important role in the treatment of this meningitis. Cefotaxime, ceftizoxime, ceftriaxone, and moxalactam have cured meningitis due to *E. coli, Klebsiella, Enterobacter,* and *Serratia* which developed in the hospital. These new agents have proved to be dramatic answers to what heretofore was a most discouraging problem. *Pseudomonas* meningitis remains a problem and the new penicillins would have to be combined with tobramycin.

Areas of No Use for the New Cephalosporins

There are nosocomial infections in which the new cephalosporins are not useful. These infections are due to *Legionella, Clostridium difficile,* most *Acinetobacter,* many *P. maltophila,* and of course the major problems associated with the fungi *Candida* and *Aspergillus.* Appropriate use of the new cephalosporins will prevent the appearance of new pathogens.

One must make serious efforts to reduce nosocomial infections, although I have pointed out why nosocomial infections will never vanish. Epidemics and some endemic disease could be further eliminated by attention to minor details of hygiene.

Summary

Nosocomial infections will continue to be a major problem during the 1980s. The types of hospitalized patients will include more patients at risk

of infection as the result of invasive medical procedures and therapy performed on the pulmonary and cardiac system. Nosocomial neonatal infection, bacteremia, and pulmonary infections are areas in which the β-lactamase stable cephalosporins will be of increasing value. The *in vitro* activity and human pharmacology of new cephalosporins made them ideal candidates to use as monotherapy for nosocomial urinary infection and skin structure and bone infections. Care in the use of the new cephalosporins must be exercised because it is probable that such species as *Enterobacter, Pseudomonas,* and *Acinetobacter* which can develop resistance to these new agents may increase. Likewise, it will be important to monitor the use of the new agents so that infections due to *Staphylococcus epidermidis, Corynebacterium JK, Streptococcus faecalis,* and fungi do not increase. The new cephalosporins are a welcome addition to the drugs which treat nosocomial infections, but will not solve the problem, and efforts to improve hospital hygiene must continue.

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